*Journal of the American College of Toxicology*
13(3):231–245, Raven Press, Ltd., New York

# Final Report on the Safety Assessment of Lauramine Oxide and Stearamine Oxide

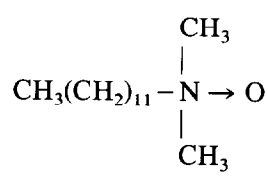
**Summary:** Lauramine Oxide and Stearamine Oxide are aliphatic tertiary amine oxides that are used mostly in hair care products as foam builders and stabilizers, viscosity enhancers, emollients, conditioners, emulsifiers, antistatic agents, and wetting agents. Both compounds are susceptible to nitrosation and can form nitrosamines in the presence of nitrosating agents. In rats, up to 40% of Lauramine Oxide applied to the skin was absorbed. In two human volunteers, 92% of the dose applied to the skin was recovered from the skin. The oral $LD_{50}$ in rats for a formulation containing 0.3% Lauramine Oxide was estimated to be >20 g/kg. At a concentration of 30%, Lauramine Oxide produced severe dermal reactions in rabbits, but at 0.3% only slight to moderate erythema with slight edema, fissuring, and slight to moderate epithelial desquamation were found. Stearamine Oxide applied to rabbit skin at 5% did not cause irritation. Both ingredients caused mild, transient ocular irritation in rabbits. Clinical data showed dermal exposure to 3.7% Lauramine Oxide to be a mild irritant, with a slight potential for mild cumulative skin irritation at concentrations as low as 2%. At 0.3%, Lauramine Oxide was not a sensitizer in clinical studies. Lauramine Oxide was nonmutagenic in the Ames assay, but was mutagenic after nitrosation. Lauramine Oxide at 0.1% in drinking water was not carcinogenic in rats, but at 0.1% with 0.2% sodium nitrate did increase the incidence of liver neoplasms. Based on this animal data, neither ingredient should contain *N*-nitroso compounds nor be used in formulations containing nitrosating agents. On the basis of the available animal and clinical data, it is concluded that Lauramine Oxide and Stearamine Oxide are safe as cosmetic ingredients for rinse-off products, but that the concentration in Lauramine Oxide leave-on products should be limited to 3.7% and that of Stearamine Oxide limited to 5%. **Key Words:** Safety assessment—Lauramine Oxide—Stearamine Oxide.

Lauramine Oxide and Stearamine Oxide are aliphatic tertiary amine oxides that are used in cosmetics as foam builders and stabilizers, viscosity enhancers, emollients, conditioners, emulsifiers, antistatic agents, and wetting agents.

## CHEMISTRY

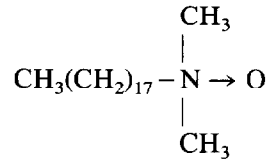
### Definition and Structure

Lauramine Oxide is the aliphatic tertiary amine oxide that generally conforms to the structure (Estrin et al., 1982; Klein, 1981):



Synonyms for Lauramine Oxide (CAS No. 1643-20-5) are: *N,N*-dimethyl-1-dodecanamine-*N*-oxide; 1-dodecanamine, *N,N*-dimethyl-, *N*-oxide; lauryl dimethyl amine oxide; dodecylamine, *N,N*-dimethyl, *N*-oxide; dimethyldodecylamine *N*-oxide; dodecyldimethylamine oxide; lauryldimethylamine oxide; and ammonyx LO (Estrin et al., 1982; Sweet, 1987).

Stearamine Oxide is an aliphatic tertiary amine oxide with the following structure (Estrin et al., 1982; Klein, 1981):



Other names for Stearamine Oxide (CAS No. 2571-88-2) include: *N,N*-dimethyl-1-octadecanamine-*N*-oxide; 1-octadecanamine, *N,N*-dimethyl-, *N*-oxide; stearyl dimethylamine oxide; and ammonyx SO (Estrin et al., 1982; Sweet, 1987).

## Properties

Lauramine Oxide is a clear, pale-yellow liquid that is typically 30–40% active, and Stearamine Oxide is a pearly white paste that is formulated to be 25% active (Hunting, 1983). The physical properties of Lauramine Oxide and Stearamine Oxide are shown in Table 1.

Both Lauramine Oxide and Stearamine Oxide are polar amine oxides that undergo hydrogen bonding. The dipole moment for the N–O bond is 4.38. Lauramine Oxide and Stearamine Oxide are hygroscopic and do not dry easily. Both compounds are stable in detergent formulations, and do not show any oxidizing properties. However, Lauramine Oxide and Stearamine Oxide are susceptible to nitrosation (Swern, 1979; Hunting, 1983). Studies of Lauramine Oxide and Stearamine Oxide indicate that these compounds have the potential to form carcinogenic nitrosamines when ingested with nitrate (Lijinsky, 1982; Lijinsky et al., 1981).

Lauramine Oxide and Stearamine Oxide have either nonionic or cationic prop-

**TABLE 1.** *Chemical and physical properties*

| | Lauramine Oxide | Stearamine Oxide | References |
|---|---|---|---|
| Molecular weight | 229.46 | 313 | Sweet (1987); Smith (1987) |
| Density | | 0.947 (at 65°C (g/ml)) | Smith (1987) |
| Viscosity 60°C, 10% aqueous (cp) | | 48 | Smith (1987) |
| $pK_a$ (1% solution) | | 3.6 | Smith (1987) |
| Solubility | Water | Ethanol, acetone; will disperse in water | Hunting (1983); Smith (1987) |
| Pour point (°C) | | 50 | Smith (1987) |
| Gel point (°C) | | 59 | Smith (1987) |

erties, depending on the pH of the aqueous solution in which they are contained. At pH 7 and above, both Lauramine Oxide and Stearamine Oxide are essentially nonionic, but below pH 3, they are primarily cationic (Devinsky, 1985; Swern, 1979; Weinstein, 1979).

### Methods of Manufacture

Lauramine Oxide and Stearamine Oxide are typically manufactured by slowly mixing each amine with 35% hydrogen peroxide at 60°C. After addition of the peroxide is complete, the temperature of the mixture is raised to 75°C. The product of this reaction is mixed with sodium sulfite or manganese dioxide, and filtered to eliminate excess peroxide. The result is a 30–40% active solution of amine oxide (Swern, 1979; Klein, 1981).

### Impurities

Lauramine Oxide may contain isopropyl alcohol, which improves fluidity (Hunting, 1983). No information is currently available concerning impurities in Stearamine Oxide.

Lauramine Oxide and Stearamine Oxide, as well as certain other amines and amides, are readily nitrosated to form nitrosamines and nitrosamides, respectively. According to the National Research Council (1983):

> Of the approximately 300 *N*-Nitroso compounds that have been tested, 85% of the 209 nitrosamines . . . and 92% of the 86 nitrosamides have been shown to produce cancer in laboratory animals (Shank and Magee, 1981; NRC, 1981). *N*-Nitroso compounds are readily formed by the interaction of nitrosating agents (nitrous acid, oxides of nitrogen, nitro compounds, and other nitroso compounds) and secondary or tertiary amines and amides. The amines and amides may be nitrosated to nitrosamines and nitrosamides under acidic, neutral, or alkaline conditions. Atmospheric $NO_2$ may also participate in the nitrosation of amines in aqueous solution (Challis et al., 1982).

Some cosmetic products formulated with Lauramine Oxide have contained nitrosamines. *N*-Nitroso-*N*-methyldodecylamine and *N*-nitroso-*N*-methyltetradecylamine were detected in hair care products, and it was assumed that Lauramine Oxide was the "likely precursor" of these nitrosamines (Hecht et al.,1982).

Thermeidics Company, Mass. (1990) reported the following nitrosamine concentrations for several formulation lots containing 30% Lauramine Oxide (Table 2).

## USE

### Cosmetic Use

#### *United States*

Lauramine Oxide and Stearamine Oxide are used in cosmetic formulations as foam builders and stabilizers, viscosity enhancers, emollients, conditioners, emul-

TABLE 2. *Nitrosamine levels in Lauramine Oxide*[a]

| Description | NDMA (ppb) | NAlkylMA | Total (ppb) |
|---|---|---|---|
| Lot 128: Sample A | 210 | 250 | 460 |
| Sample B | 119 | 138 | 257 |
| Lot 65: Sample A | 294 | 128 | 422 |
| Lot 44: Sample A | 381 | ND | 381 |
| Sample B | 373 | ND | 373 |
| Detection limit | 20 | 80 | |

NDMA, nitrosodimethylamine; NAlkylMA, nitrosoalkylmethylamine.
[a] No data on nitrosamines in Stearamine Oxide are currently available.

sifiers, antistatic agents, and wetting agents (Klein, 1981; Nikitakis, 1988; Smith et al., 1987).

The product formulation data submitted to the Food and Drug Administration (FDA) in 1992 reported that Lauramine Oxide and Stearamine Oxide were used in a total of nine and 37 cosmetic product formulations, respectively (Tables 3 and 4) (FDA, 1992).

Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, product formulation data submitted to the FDA in 1989 stated that Lauramine Oxide was used at concentrations <1% in hair rinses, tonics, dressings, and other hair grooming aids, and at up to 10% in shampoos (FDA, 1989). Data submitted in 1984 indicated that Stearamine Oxide was used at up to 10% in hair conditioners and shampoos, and up to 5% in hair rinses and other skin care preparations (FDA, 1984).

### *International*

Lauramine Oxide and Stearamine Oxide solutions are approved for use in cosmetic products in Japan (Nikko Chemicals Co., Ltd., 1990).

### Noncosmetic Use

Lauramine Oxide and Stearamine Oxide are used as light duty liquid detergents, and oil sequestering agents in industry (Smith et al., 1987; Oyewo, 1986; Thorhaug and Marcus, 1987).

## BIOLOGY

### Absorption, Metabolism, Excretion, and Distribution

Two groups of four male and one group of four female Sprague–Dawley rats were given 100 mg/kg of [methyl-$^{14}$C]Lauramine Oxide (specific activity 1.3 mCi/g) or [1-dodecyl-$^{14}$C]Lauramine Oxide (specific activity 1 mCi/g) orally in a metabolic study. There were no significant differences in metabolism or distribution of the compounds between male and female rats. Approximately 75% of the total radioactivity was excreted within 24 h of oral administration. The rats eliminated 71 and 53% of the administered dose of [methyl-$^{14}$C]Lauramine Oxide and [1-dodecyl-$^{14}$C]Lauramine Oxide, respectively, in their urine, 13 and 23% as $^{14}CO_2$, and 12 and 9% in their feces. Over two-thirds of the radioactivity expired as $^{14}CO_2$

TABLE 3. *Cosmetic product formulation data for Lauramine Oxide (FDA, 1992)*[a]

| Product category | Total no. of formulations in category | Total no. of formulations containing ingredient |
|---|---|---|
| Hair rinses (noncoloring) | 83 | 3 |
| Hair shampoos (noncoloring) | 953 | 3 |
| Tonics, dressings, and other hair grooming aids | 548 | 3 |
| 1992 totals | | 9 |

[a] CIR requests that the cosmetic industry provide current formulation data on each product category.

appeared within 12 h after administration of either dose. The largest concentration of radioactivity in the tissue was found in the liver. Radioactivity was also found in the kidneys, intestine, lungs, spleen, heart, pancreas, bone marrow, leg muscles, testes, ovaries, and whole blood (Rice, 1977).

Aqueous [methyl-$^{14}$C]Lauramine Oxide (10 mg containing 1.3 mCi/g) was applied to the skin of four Sprague–Dawley rats to test metabolism and absorption of the compound. Over 72 h, 14.2% of the total radioactivity was found in the urine, 2.5% in the $CO_2$, and 1.8% in the feces. Radioactivity was detected in the liver, kidneys, testes, blood, and expired $CO_2$ (Rice, 1977).

In a similar study, aqueous [methyl-$^{14}$C] Lauramine Oxide (10 mg containing 13 μCi radioactivity) was applied to the skin of four rats. Approximately 40% of the total radioactivity was absorbed through the skin. Fourteen percent of the radioactivity was excreted in the urine, 2.5% was recovered as $^{14}CO_2$, and 1.8% was eliminated in the feces (Drotman, 1977).

Four Sprague–Dawley rats were given intraperitoneal injections of 22 mg [methyl-$^{14}$C]Lauramine Oxide/kg (specific activity 1.3 mCi/g). Sixty-seven percent of the total radioactivity was eliminated in the urine, 8% was expired as $^{14}CO_2$, and 6% was eliminated in the feces within 24 h. The distribution of radioactivity was essentially the same as that seen in rats given oral doses of Lauramine Oxide. The conclusion was that ". . . microbial metabolism by gastrointestinal flora does not play a major role in the absorption and excretion of [Lauramine Oxide] in rats" (Rice, 1977).

Oral administration of a solution containing 50 mg [1-dodecyl-$^{14}$C]Lauramine Oxide (100 μCi of $^{14}$C) to two humans resulted in excretion patterns of radioac-

TABLE 4. *Cosmetic product formulation data for Stearamine Oxide (FDA, 1992)*[a]

| Product category | Total no. of formulations in category | Total no. of formulations containing ingredient |
|---|---|---|
| Hair conditioners | 666 | 18 |
| Hair rinses (noncoloring) | 83 | 5 |
| Hair shampoos (noncoloring) | 953 | 9 |
| Other skin care preparations | 848 | 5 |
| 1992 totals | | 37 |

[a] CIR requests that the cosmetic industry provide current formulation data on each product category.

tivity similar to that of the other species studied. Fifty percent and 37% of the radioactivity was found in the urine within 24 h of dosing, and expired $^{14}CO_2$ contained between 18 and 22% of the radioactivity administered (Rice, 1977).

[1-dodecyl-$^{14}$C]Lauramine Oxide (10 mg with 100 μCi of $^{14}$C) was applied to the skin of two humans to study cutaneous absorption and metabolism of Lauramine Oxide. Ninety-two percent of the applied radioactivity was recovered from the skin of the test subjects 8 h after dosing, and 0.1 and 0.23% of the radioactivity was recovered from the excretion products of the test subjects. The stratum corneum contained <0.2% of the applied dose (Rice, 1977).

Characterization of metabolites of Lauramine Oxide resulted in the positive identification of only one metabolite, *N*-dimethyl-4-aminobutyric acid *N*-oxide. Several pathways exist for metabolism of Lauramine Oxide: ω,β-oxidation of alkyl chains (the most common pathway for surfactant metabolism), hydroxylation of alkyl chains, and reduction of the amine oxide group (Turan and Gibson, 1981).

Metabolic profiles for different species (rat, human, mouse, rabbit) did not have any significant differences in metabolites, but the degree of absorption, especially in cutaneous applications, varied from species to species (Drotman, 1977; Rice, 1977).

## ANIMAL TOXICOLOGY

### Acute Toxicity

#### *Oral*

The estimated oral $LD_{50}$ of a formulation containing Lauramine Oxide was determined using the up–down and limit test procedures. An undiluted formulation containing 0.3% active Lauramine Oxide was administered by gavage to six female CD Sprague–Dawley rats at doses of 20 g/kg or greater. All animals survived to termination. No adverse signs were observed (Oak Ridge Research Institute, 1989a).

In similar studies, the $LD_{50}$ was >25.0 ml/kg and >10.0 g/kg for two other formulations containing 0.3% active Lauramine Oxide. Groups of three female and three male albino Sprague–Dawley rats were used to evaluate each product. All animals survived to termination, and no significant clinical or pathologic abnormalities were observed (Hazelton Laboratories America, Inc., 1985).

Five male and five female Charles River rats were given 5 g/kg doses of a 20% dilution of Stearamine Oxide by stomach tube. The animals were observed daily, and were killed on day 14. All animals survived to termination and no signs of toxicity were observed. No macroscopic changes were reported in any of the internal organs (Leberco Testing, Inc., 1985).

#### *Inhalation*

The acute inhalation toxicity of a liquid droplet aerosol formulation containing 0.3% active Lauramine Oxide was evaluated. Five female and five male albino

Sprague–Dawley–derived rats were exposed for 4 h to this aerosol at a concentration of 5.3 mg/L. The Equivalent Aerodynamic Diameter of the aerosol was 3.6 μm with a geometric standard deviation of 1.91. The animals were observed during the exposure and two times daily for 14 days, and body weights were recorded before exposure and on days 1, 3, 7, and 14 postexposure. At necropsy, the major organs in the abdominal and thoracic cavities were weighed and observed.

No deaths occurred during the study and all the rats appeared normal. A slight drop in body weight was observed in the males on day 1, but weight was gained normally for the remainder of the study. The weight gain in the females was normal. The organ weights were all within the anticipated normal control ranges for both sexes. No exposure-related pharmacotoxic signs were evident in any of the organs. The 4-h $LD_{50}$ for this aerosol was greater than 5.3 mg/L nominal (International Research and Development Corporation, 1990a).

The potential for this same formulation to produce upper airway irritation in mice was also studied. Liquid droplet aerosols at concentrations of 0.2, 1.0, and 5.2 mg/L were tested on three groups of four male Swiss–Webster mice. Only the heads of the mice were exposed to the aerosol. The average respiratory rate was monitored using plethysmography 5 min before, 10 min during, and 10 min after each exposure, and the percentage change in respiratory rate was calculated. A decrease in respiratory rate was considered a response to upper airway irritation.

A transient decrease was observed in the respiratory rate of the 1.0 mg/L exposed group, but this was not considered significant because no signs of irritation were seen at greater exposure concentrations. The groups treated with 1.0 mg/L and 5.2 mg/L had a 6% decrease in their average respiratory rates. However, these decreases were not attributed to upper airway irritation because the respiratory rates were even lower during the postexposure recovery period. No decrease in respiratory rate was observed in the 0.2 mg/L exposed mice (International Research and Development Corporation, 1990b).

### Subchronic Dermal Toxicity

New Zealand White rabbits were used to assess the cutaneous and systemic toxicity of a formulation containing 0.3% active Lauramine Oxide. The abraded skin of five female and five male rabbits was exposed to the formulation five times a week for 4 weeks. The dosage was 2 ml/kg/day. A control group of five female and five male rabbits was exposed to distilled water. All animals survived to termination. No significant differences in mean body weights, body weight changes, clinical observations, mean absolute organ weights, or organ-to-body weight ratio between the treated and control groups were observed. Lauramine Oxide caused slight to moderate erythema in female rabbits, and both male and female rabbits had slight edema, atonia, and fissuring, and slight to moderate desquamation. Histologically, both groups had a high incidence of subacute inflammation in the treated skin. The lesions were described as ". . . minimal infiltrations of lymphocytes with a few neutrophils and plasma cells in the superficial dermis." Two cases of epidermal acanthosis, one case of crusting, and one

case of superficial dermal hemorrhage were also observed (Hazelton Laboratories America, Inc., 1990).

### Dermal Irritation

The primary dermal irritation potential of three formulations, each containing 30% Lauramine Oxide, was evaluated using New Zealand White rabbits. Three male and three female rabbits had 0.5 ml of each formulation applied under occlusive patches to separate sites on their clipped backs for 24 h. The sites were rinsed after patch removal and were scored for erythema, eschar, and edema at the time of removal and 48 h later. The primary dermal indices (maximum possible score: 8) were 7.0, 7.2, and 7.6. Moderate to severe erythema and edema, two cases of necrosis, and one case of necrosis and fissuring with bleeding were observed at the 24-h grading period. At the 72-h reading, there was severe erythema and edema, eschar, fissuring with bleeding, and necrosis and/or thickened skin (Ricerca, Inc., 1988).

The dermal irritation potential of Stearamine Oxide was conducted on albino rabbits in accordance with the Code of Federal Regulations 21, Part 191.1 (g) (2), 191.11. Patches of 5% active Stearamine Oxide (0.5 ml) were applied to the intact and abraded skin of six rabbits for 24 h. The application sites were graded at the time of removal and 48 h later. No signs of irritation were observed at any time during the study (Leberco Laboratories, 1973).

Like et al. (1975) reported that Stearamine Oxide (5% active) was not a primary irritant when tested using the methods of Draize (1959).

### Ocular Irritation

The ocular irritation potential of formulations containing 0.3% active Lauramine Oxide was evaluated by instilling 10 μl into the conjunctival sac of New Zealand White rabbits. The eyes of some rabbits were rinsed with distilled water. Irritation was scored according to the method of Draize (1959) (maximum possible score: 110). Slight irritation of the conjunctivae was observed in all unrinsed eyes and in two of three rinsed eyes at the 24-h grading period. The maximum average score was 2.0 for the animals with unrinsed eyes, and 1.3 for those whose eyes were rinsed. All eyes were clear after 48 h (Springborn Life Sciences, Inc., 1987).

In other studies using Lauramine Oxide, no irritation was observed. The maximum average score was 0 for both the rinsed and unrinsed eyes (Oak Ridge Research Institute, 1989b; Hazelton Laboratories America, Inc., 1986).

Stearamine Oxide was tested for ocular irritation according to the methods of Draize (1959). A 5% active sample of Stearamine Oxide (pH 7.5, dose 0.1 ml) was instilled into the conjunctival sac of three albino rabbits. The eyes were examined 24, 48, and 76 h after instillation. Minimal eye irritation was reported. At the 24-h grading period, two of the rabbits had redness of the conjunctiva, and one of these also had chemosis. The average eye irritation score was 2.67. No irritation was seen after 24 h (Industrial Biology Laboratories, Inc., 1963).

Like et al. (1975) reported that Stearamine Oxide (5% active) was not an ocular irritant when tested using the methods of Draize (1959).

## MUTAGENICITY

Lauramine Oxide and its nitrosation products were tested for mutagenicity by Andrews et al. (1984) using the Ames test (Ames et al., 1975). Modifications of the Ames test were 0.2 ml of the tester strain instead of 0.1 ml, 20 ml of the VBE medium instead of 30 ml, and the Aroclor 1254–stimulated microsome S9 mix was used at a level of 75 μl of S9 fraction/test. Assays were conducted using Lauramine Oxide (250 μg) alone and Lauramine Oxide reacted with nitrite in an acid solution (to simulate nitrosation reactions that may occur in the stomach). Test strains of *Salmonella typhimurium* used were TA1535, TA1538, TA98, and TA100. Each test was conducted both with and without metabolic activation by S9 liver microsome fractions. Lauramine Oxide alone was not mutagenic, either with or without activation. The nitrite treated Lauramine Oxide activated with the S9 liver microsome fraction was mutagenic to strain TA-1535. Significant quantities of nitrosomethyldodecylamine were formed when Lauramine Oxide was reacted with an excess of sodium nitrite in solution at pH 3.5. The authors pointed out that nitrosomethyldodecylamine is a known mutagen to strain TA-1535 *S. typhimurium* (Andrews et al., 1978).

In another study, Lauramine Oxide and *N*-nitrosomethyl-*n*-dodecylamine were evaluated for mutagenicity using modified Ames test methods (Ames et al., 1975) with *S. typhimurium* strains TA98 and TA100. Lauramine Oxide, at doses ranging from 10 to 200 μg/plate, was not mutagenic with or without S9 activation. However, *N*-nitrosomethyl-*n*-dodecylamine, tested at doses ranging from 50 to 5,000 μg/plate, caused significant but low mutagenic activity in TA100 after metabolic activation (Inoue et al., 1980).

## CARCINOGENICITY

An in vitro cell transformation assay was used to assess the carcinogenic potential of Lauramine Oxide. Cryopreserved primary cultures of Syrian golden hamster embryo cells were used as the source of target and feeder cells. Lauramine Oxide, at doses of 0.1, 1, 5, 10, and 20 μg/ml, did not cause transformation (Inoue et al., 1980).

Lijinsky (1984) conducted feeding studies to determine the carcinogenicity of Lauramine Oxide and its nitrosated products. Two groups of 24 male and 24 female F344 rats were given drinking water supplemented with 0.1% Lauramine Oxide alone or with 0.1% Lauramine Oxide plus 0.2% sodium nitrite for 93 weeks. Positive control rats were given drinking water with 0.2% sodium nitrite, and untreated control rats were given unsupplemented water. There was no significant difference in survival between the treated and untreated groups of male rats. For the females, those treated with Lauramine Oxide alone died significantly earlier than those treated with nitrite alone or with Lauramine Oxide plus sodium nitrite. No other differences in survival were observed between the female groups.

There was a significant increase in the incidence of hepatic neoplasms (hepatocellular carcinomas and neoplastic nodules) in the male rats receiving Lauramine Oxide and nitrite. No significant increase in hepatic neoplasms was observed in rats receiving Lauramine Oxide alone. The authors concluded that

Lauramine Oxide with sodium nitrite in the drinking water of male rats ". . . results in the formation of at least one carcinogenic nitrosamine which is responsible for the increased incidence of liver neoplasms."

The carcinogenicity of the nitrosation products of Lauramine Oxide (nitrosodimethylamine, *N*-nitroso-*N*-methyldodecylamine and *N*-nitroso-*N*-methyltetradecylamine) has been documented in studies by The National Research Council, Committee on Nitrite and Alternative Curing Agents in Food (1981); Ketkar et al. (1981); Lijinsky et al. (1981); Cardy and Lijinsky (1980); Althoff and Lijinsky (1977); Lijinsky and Taylor (1975); and Magee and Barnes (1956).

## CLINICAL ASSESSMENT OF SAFETY

### Dermal Irritation

The irritancy of Lauramine Oxide was tested using ten volunteer subjects. Each subject was patch tested with a 3.7% aqueous solution of Lauramine Oxide. Five of the tested individuals had mild irritation 48 h after exposure. These subjects were exposed a second time in an open test, and no irritation occurred (Muston et al., 1977).

The cumulative irritancy potential of Lauramine Oxide was also tested. Ten subjects had 1.0, 2.0, 3.0, 4.0, and 5.0% Lauramine Oxide applied to their backs on Monday, Wednesday, and Friday for 48 h. A total of three consecutive applications was made. The sites were scored at the time of each patch removal. Scoring was based upon a standardized interpretation system for ten panelists' irritation scores for 21 days, which was modified to account for three applications rather than 21. Scores were determined by totalling the three observation scores for each site. The maximum possible score was 90. The authors classified 1.0% Lauramine Oxide as having no cumulative irritation with a score of 4.5. At concentrations of 2.0, 3.0, 4.0, and 5.0%, Lauramine Oxide had cumulative irritation scores of 10.5, 11.5, 15.0, and 24.0, respectively, which were considered evidence of a slight potential for very mild cumulative irritation (In Vitro Alternatives, Inc., 1992a).

### Dermal Sensitization

A formulation containing 0.3% active Lauramine Oxide was diluted to a 50% (w/v) solution with distilled water and was tested for allergic contact sensitization potential using repeated occlusive patch application procedures. Patches with 0.5 ml of the diluted formula were applied every Monday, Wednesday, and Friday for 3 weeks to the lateral surface of the upper arm. The 101 participants removed the patches 24 h after application, and the patch sites were graded before the application of the new patch. The challenge patches were applied ~17 days after the last induction application, and the sites were graded 48 and 96 h after patch removal.

Twenty-four of the participants had reactions during the induction phase of the test. Of these, 14 had single reactions, seven had two reactions, one had four

reactions, and two had six reactions. All of the reactions during the induction phase were described as Grade 1, very mild erythematous responses. In addition, two of these participants had barely perceptible reactions at the original patch sites during the challenge phase (one during the 48-h grading, and the other at both the 48- and 96-h grading periods). The formulation containing Lauramine Oxide did not cause sensitization (Harris Laboratories, Inc., 1987).

Using the same methodology with 84 volunteers, another formulation containing 0.3% active Lauramine Oxide was diluted to a 50% aqueous (w/v) solution and was tested for its skin sensitization potential. Slight irritation was observed in nine individuals during the induction phase. During the challenge phase, four participants had slight erythema (one at the original patch site, and three on the alternate site) at the 48-h grading period, and only one individual had mild irritation at the original site during the 96-h grading period (CTFA, 1986).

Standard repeat insult patch methodology also was used to study another cosmetic formulation containing 0.3% active Lauramine Oxide. Occlusive patches containing 0.3 ml of a 10% (w/v) solution of this formulation with distilled water were applied to the skin of 107 individuals for 24 h. During the challenge phase, four individuals had mild erythema, and one had both erythema and mild edema. This latter individual was rechallenged at both the original and alternate sites. Patches of distilled water and 0.5% sodium lauryl sulfate were also applied at these sites to serve as negative and positive controls, respectively. All the patches were applied for 24 h and the sites were scored 48 and 96 h after application. The subject had mild erythema at the original and alternate patch sites treated with the experimental sample, and at the alternate site of the positive control sample at the 48-h grading period. All signs of irritation disappeared by 96 h. Consequently, no evidence of delayed contact hypersensitivity to this formulation was observed (Hill Top Research, Inc., 1989).

In a similar study, 141 subjects were tested with 1.5% Lauramine Oxide during the first six induction exposures, and with 0.75% Lauramine Oxide for the last three induction exposures and for the challenge exposure. The concentration of Lauramine Oxide was reduced because several of the participants had mild irritation. The application sites were scored (on a scale of 0–3) 48 and 96 h after the challenge exposure. At the 48-h reading period, 46 individuals received scores of 0.5, 12 received scores of 1, and two received scores of 2. At the 96-h reading, six individuals had scores of 0.5. According to the authors, these scores were the same as those observed during induction, and were indicative of primary and cumulative irritation rather than a delayed reaction. Lauramine Oxide was not considered a sensitizer under these test conditions (In Vitro Alternatives, Inc., 1992b).

## SUMMARY

Lauramine Oxide and Stearamine Oxide are used in cosmetics as foam builders and stabilizers, viscosity enhancers, emollients, conditioners, emulsifiers, antistatic agents, and wetting agents. Lauramine Oxide was reported to contain up to 460 ppb of carcinogenic *N*-nitrosamines. Data regarding the contamination of Stearamine Oxide with such impurities were not available.

The major route of excretion following oral and dermal doses of Lauramine Oxide was through the urine. Excretion patterns were similar between test animals and human subjects. Lauramine Oxide was absorbed through the skin in varying amounts depending on the test animal. In rats, 14–40% of the applied dose was absorbed, whereas Lauramine Oxide was absorbed to a much lesser extent in studies with humans. The only metabolite that was identified was *N*-dimethyl-4-aminobutyric acid *N*-oxide.

The oral $LD_{50}$ for a formulation containing 0.3% active Lauramine Oxide was estimated to be >20 g/kg for Sprague–Dawley rats. Inhalation assays with mice and rats indicated only minor, acute toxic effects for Lauramine Oxide. Lauramine Oxide was not dermally toxic to rabbits.

Formulations containing 30% Lauramine Oxide were moderately to severely irritating to the skin of rabbits. Dermal exposure to 5% active Stearamine Oxide did not cause irritation in rabbits.

In human studies, Lauramine Oxide tested at up to 3.7% was a mild irritant and showed a slight potential for very mild cumulative irritation at concentrations between 2.0 and 5.0%. However, 0.3% active Lauramine Oxide was not a sensitizer.

Lauramine Oxide and Stearamine Oxide caused mild, transient ocular irritation in rabbits.

Lauramine Oxide was not mutagenic in the Ames test; however, when this ingredient was reacted with nitrite, the resulting nitrosation product was mutagenic with metabolic activation. In a feeding study, male rats given drinking water with Lauramine Oxide (0.1%) and sodium nitrite had an increase in hepatic neoplasms. The nitrosation products of Lauramine Oxide are known carcinogens. Lauramine Oxide alone at 0.1% in drinking water did not cause hepatic neoplasms in rats.

## DISCUSSION

Although data on Stearamine Oxide are limited, the CIR Expert Panel agreed that the more substantive information on Lauramine Oxide was applicable to the evaluation of Stearamine Oxide because the two ingredients are chemically similar. The potential for Lauramine Oxide and Stearamine Oxide to form nitrosamines is significant. The Expert Panel cautions that the ingredients should not contain *N*-nitroso compounds, and that cosmetic products containing Lauramine Oxide and Stearamine Oxide should be free of nitrosating agents.

Lauramine Oxide and Stearamine Oxide are mild irritants and have the potential for mild cumulative irritation. Based upon the concentrations tested in the available dermal studies, the Expert Panel recommended that the use of Lauramine Oxide and Stearamine Oxide be limited to 3.7 and 5%, respectively, in cosmetic products intended for leave-on use.

## CONCLUSION

On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that Lauramine Oxide and Stearamine Oxide are

safe as cosmetic ingredients for rinse-off products under present conditions of use. For use in leave-on products, the Expert Panel concludes that Lauramine Oxide should be limited to 3.7% and Stearamine Oxide to 5%.

**Acknowledgment:** Susan N. J. Pang, Scientific Analyst and Writer, prepared this report.

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